Asbestos, Asbestosis, and Lung Cancer: Observations in Quebec Chrysotile Workers

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One prospective epidemiologic study of asbestos cement workers with radiological small opacities has been cited as a rationale for attributing excess lung cancer to asbestosis. This approach could have considerable practical value for disease attribution in an era of decreasing exposure. However, a recent International Agency for Research on Cancer review concludes that the mechanisms of production of asbestos-related lung cancer are unknown. Asbestosis, therefore, cannot be a biologically effective dose marker of lung cancer susceptibility. Asbestosis nonetheless would be useful in identifying asbestos-attributable lung cancer cases if it could be proven an infallible exposure indicator. In this study, we tested this hypothesis in the chrysotile miners and millers of Quebec, Canada. We examined exposure histories, autopsy records, and lung fiber content for 111 Quebec chrysotile miners and millers. If the hypothesis of an asbestosis requirement for lung cancer attribution were accurate, we would expect an asbestosis diagnosis to separate those with lung cancer and high levels of exposure from those with lower levels of exposure in a specific and sensitive manner. This is the first such study in which historical job-based individual estimates based on environmental measurements, lung fiber content, exposure timing, and complete pathology records including autopsies were available for review. We found significant excesses of lung tremolite and chrysotile and estimated cumulative exposure in those with lung cancer and asbestosis compared to those with lung cancer without asbestosis. However, when the latter were directly compared on a case-by-case basis, there was a marked overlap between lung cancer cases with and without asbestosis regardless of the measure of exposure. Smoking habits did not differ between lung cancer cases with and without asbestosis. In regression models, smoking pack-years discriminated between those with and without lung cancer, regardless of asbestosis status. Most seriously, the pathologic diagnosis of asbestosis itself seemed arbitrary in many cases. We conclude that although the presence of pathologically diagnosed asbestosis is a useful marker of exposure, the absence of this disease must be regarded as one of many factors in determining individual exposure status and disease causation. — *Environ Health Perspect* 105(Suppl 5):1113–1119 (1997)

Key words: asbestos, asbestosis, lung cancer, compensation, causation, lung burden, disease mechanisms, exposure assessment, risk assessment, attributable risk

Introduction

Early in the twentieth century, pathologists and clinicians recognized that asbestos causes pulmonary fibrosis (*1*). Exposure levels at that time were very high—in most industries much higher than 100 fibers/ml (*2*). Asbestosis was made a reportable disease in some jurisdictions so that all cases were autopsied (*1*). As lung cancer cases (then rare) were noted and recorded among these men and women, medical observers began to suspect a link between lung cancer and asbestosis. Because asbestosis cases were preferentially evaluated (as opposed to cases with asbestos exposure), a causative link was suspected between the two diseases. Lynch and Smith suggested in 1935 that this type of lung cancer might arise "by reason of chronic bronchial irritation" (*1*). With the advent of true analytical epidemiologic study between 1955 and 1964, the causal relationship between asbestos exposure and lung cancer became established (*1*). The earlier thought that asbestosis, or fibrotic disease of the lung parenchyma, could cause carcinoma of bronchial origin was set aside. It was realized that both asbestosis and lung cancer were dose related, with the resulting collinearity creating the appearance of a relationship between the two.

This view remains widely accepted by biological scientists in the field today (*3*), but one epidemiologic study of a small number of Louisiana asbestos cement workers has provoked renewed discussion (*4*), particularly in the context of asbestos litigation and compensation. This study found that of seven excess lung cancers in this group of workers, all had radiological small opacities graded 1/0 or greater on the International Labour Organisation scale ($p < 0.05$, if using a one-tailed test).

Cigarette smoking contributes to lung cancer risk in those with heavy asbestos exposure in an as yet poorly understood manner, which is more than additive but probably less than multiplicative. This has led to further speculation as some medical scientists attempt to separate asbestos-attributable cases from those due entirely to smoking.

There is little literature on this subject to address the hypothesis of Hughes and Weill that asbestosis is a necessary precondition for lung cancer (*4*). The methodological flaws in Hughes and Weill's study, as outlined by Egilman and Reinert (*5*), have been largely overlooked as the results were reprinted in textbooks, journal supplements, and symposium proceedings.

A larger hospital-based case–control study of a more heterogeneous group of lung cancer cases and controls in the United Kingdom (*6*) had opposite results. Both crude and adjusted odds ratios (for age, sex, smoking, and referral area) were increased for those with a history of definite or probable asbestos exposure regardless of asbestosis status. Again, radiological small opacities were used as the measure of asbestosis. A particularly convincing refinement eliminated bias by blinding radiologists to the portion of the lung that contained the tumor. After adjustment, the 95% CIs on the odds ratios for lung cancer for those with and without asbestosis were 1.00 to 4.73 and 1.02 to 2.39, respectively.

An autopsy study of pathologic asbestosis and lung cancer in South African amosite miners (*7*) is often cited as evidence for the Hughes and Weill hypothesis (*4*). Scrutiny, however, shows that in the first regression model used, duration of exposure produced an increment of risk even when smoking

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Abbreviations used: IARC, International Agency for Research on Cancer; MPCFY, million particles foot^3×years.

and asbestosis were accounted for. This was so although asbestosis is colinear with duration of exposure.

A histopathologic study of insulation workers in the United States (*8*) suggested that radiological asbestosis was absent in 15% of lung cancer cases. However, every lung cancer case in the population of workers had histologic lung fibrosis (not necessarily qualifying as asbestosis). Thus, lung fibrosis rather than asbestosis was an inevitable consequence of exposure as rated (perhaps liberally) by the pathologist in this study.

One reason for a lack of agreement on this question has been the paucity of data sets including exposure measurements, lung burden data, and pathologic records. Assessment of both exposure (using environmental measures) and retained dose (using lung-fiber analysis) are possible, along with direct pathologic confirmation of asbestosis rather than the radiological surrogate. Chrysotile miners and millers pose a particularly relevant test population, since the slope of the lung cancer–exposure relationship in this group is more shallow than that observed in other industrial cohorts (*9,10*). Workers in this industry who smoke are especially likely to have their lung cancer status challenged in legal or compensation hearings because of the very high levels of exposure believed to be necessary to produce disease (*10*).

The Quebec, Canada, birth cohort of approximately 11,000 chrysotile miners and millers (*9,10*) is the largest scientific resource available for the study of asbestos-related diseases. The cohort consists of all employees of the chrysotile mines and mills born between 1891 and 1920, provided they worked for at least one month. The first observations of 2413 deaths were recorded to 1966. By 1993, the most recent update of mortality, over 8000 had died (AD McDonald, personal communication).

In the current study, we examined exposure and disease variables in 111 members of this cohort who had died and had autopsies in two local hospitals. We attempt to determine to what degree pathologic asbestosis as recorded in autopsy reports predicts exposure excess in cases with and without lung cancer and/or asbestosis. Both environmental [million particles foot^3 × years worked (MPCFY)] and retained dose (fibers/μg dry lung, longer than 5 μm, aspect ratio > 3:1) measures served as gold standards for exposure. Our working hypothesis was that while grouped exposure indices would certainly be higher in cases with asbestosis with or without lung cancer, individual values might overlap considerably.

Methods

Subjects

Case selection procedures for the two previous studies (*11,12*) that provide the subject matter for the present analysis are outlined in Table 1. Lung cancer cases analyzed represent a small fraction of those that occurred in the cohort, although lung cancer constituted a higher proportion of autopsies than a normal disease distribution would produce [Table 1; (*10,13*)]. Autopsy selection bias is always a possibility in such studies (see "Discussion").

Subjects from the birth cohort in the current study were men from two separate areas of the Quebec mines and mills—Asbestos and Thetford Mines/Black Lake [Table 1; (*11,12*)]. Twenty-six cohort members at the Jeffrey Pit in Asbestos, Quebec, had consecutive autopsies from 1979 through 1983 at the Sherbrooke University Hospital (Sherbrooke, Quebec). Twenty-three had lung tissue samples available, and these were selected for our previous study of occupational and environmental lung burden in this area (*11*). One case was omitted from the current study because of an ambiguous diagnosis of lung cancer. Lung tissue samples were obtained from 215 of 302 consecutive cohort autopsies in the hospital in Thetford Mines performed between 1963 and 1984 (*12*). Because of limited resources, only 89 of these could be analyzed. These were selected ad hoc and compared to a group of South Carolina textile workers who worked with chrysotile imported from the Thetford area, in an attempt to validate MPCFY differences between the two groups (*12*).

Exposure Assessment. Exposure parameters were available from the cohort studies (*9–12*). As described previously (*9,10*), these estimates were obtained putting "much emphasis ... on the optimal use of all available dust measurements to evaluate for each cohort member his exposure to asbestos dust in terms of duration, intensity, and timing" (*10*). From the first job of the first man in 1904, detailed work histories were constructed for more than 5000 separate jobs. From 1949 to 1966, environmental midget impinger particle samples (4500 in all) were taken and recorded in every operation each year. Exposure after 1966 was considered to have added little in quantity (*9*), and would have had questionable relevance for cancer etiology. Measurements could be applied to each man in each job as MPCFY for a given job and duration, less periods of vacation or illness. This is a measure of total particles rather than fibers; although an exact conversion to fibers/ml has wide confidence limits, the best estimates were that 100 MPCFY would correspond to

Table 1. Selection of cases for this study.

	Chrysotile workers at the Jeffrey Pit, Asbestos, Quebec	Chrysotile workers in the Thetford Mines/Black Lake area
Number of cohort deaths eligible in both areas	1910–1976: 4463 deaths; 1976–1 January 1989: 2827 deaths; 1989–present: over 1000 deaths; year-by-year breakdown not available	
Hospital	University Hospital, Sherbrooke[a,b]	Asbestos Regional Hospital Centre[a]
Years of death of cases studied	1979–1983 (*11*)	1963–1984 (*12*)
Autopsies	26	302
Number of autopsies for which lung samples obtained	23	215
Number of lung samples analyzed	22[b]	89
Selection criteria for samples choesn for analysis	None [consecutive cases (*11*)]	Ad hoc (*12*)
Number and percentage of study cases with asbestosis	10 of 22 (46%)	57 of 89 (64%)
Number and percentage of study cases with lung cancer	4 of 22 (18%)[b]	22 of 89 (25%)
Number of lung cancer cases with asbestosis	2 of 4	17 of 22

[a]These hospitals accounted for approximately two-thirds of all cohort autopsies (*12*). [b]One case of lung cancer in an Asbestos region autopsy is excluded from the present study due to ambiguous diagnosis.

between 300 and 400 fiber-years. Smoking data were obtained in 1970 for surviving cohort members by self-administered questionnaires. By the end of 1988, two-thirds of the workers followed in the study had died (*10*).

Pathologic and Other Data. Asbestosis was determined by examination of autopsy reports (BW Case, personal observation) rather than death certificates, which tend to underestimate this disease (*13*). Any mention of asbestosis was accepted. It was possible in theory to grade asbestosis as mild, moderate, or severe from reports based on modifiers provided by pathologists, as was done by Sluis-Cremer and Bezuidenhout (*7*). However, since criteria for the use of these modifiers were unspecified, only the presence or absence of asbestosis were used. In all instances, pathologists recorded their opinions about whether asbestosis was present or absent. Asbestosis determination at autopsy for men from the mine and mill at Asbestos was performed by pathologists at the Sherbrooke University Hospital. At the Thetford Mines hospital, a single pathologist carried out most asbestosis determinations; he performed autopsies on well over 1000 chrysotile miners and millers.

Autopsy rates in the total cohort to 1976 were reported to be over 50% for lung cancer and asbestosis (*9*) but only 17% for men without these diseases. Mesothelioma cases had an even higher autopsy rate (*10*). Smoking histories were obtained from cohort records for most of the cases from the Thetford Mines Hospital, and pathologic indices of previous asbestos exposures (e.g., pleural plaques and asbestos bodies seen in routine sections) were recorded from autopsy reports.

Fiber Analysis and Reporting of Comparisons. Lung fiber analysis was performed according to our previously published procedures (11,12). Concentrations of all fiber types were determined using quantitative analytical transmission electron microscopy, with fiber identification by morphological examination, energy-dispersive X-ray diffraction, and selected area electron diffraction. Polarized light microscopy was used to assess total uncoated fibers in Thetford Mines (12). Fibers were counted only if their aspect ratio was greater than 3:1 and their length greater than 5 μm. Comparisons in Table 2 and in the results noted below are of median or mean values, with tests of significance provided by the Mann-Whitney or two-sample t-test. Total lung retained asbestos fiber (Figure 1) was ascertained by addition of values for tremolite, chrysotile, crocidolite, and amosite fibers longer than 5 μm with aspect ratios greater than 3:1.

Results

We examined the results for all cases combined, for the Thetford Mines cases alone (Table 2), and for each individual (Tables 3, 4; Figures 1, 2).

Of the total of 111 chrysotile miners and millers in this analysis, 19 had lung cancer with asbestosis, 7 had lung cancer without asbestosis, 45 had asbestosis alone, and 40 had neither disease. Age distribution was similar in men with asbestosis alone (68 ± 7), asbestosis with lung cancer (68 ± 7), and with neither disease (69 ± 7). The seven men with lung cancer alone were on average slightly younger (65 ± 3), although this difference was significant only versus men with neither disease ($p < 0.05$, two-sample *t*-test).

Men with both asbestosis and lung cancer had the highest median total asbestos fiber lung content (55 fibers/μg dry lung, longer than 5 μm, aspect ratio greater than 3:1, $p < 0.01$ vs all other groups). Men with asbestosis alone had the next highest intrapulmonary fiber levels (41 fibers/μg dry lung; $p < 0.01$ vs both groups without asbestosis). Men without asbestosis, regardless of lung cancer status, had significantly lower median levels of lung fiber as a group (see below). Those with lung cancer alone or with neither disease had median values of 11 and 7.5 fibers/μg dry lung, respectively (not significant).

Similar results were obtained for comparisons of the four groups using the

Table 2. Characteristics of 22 Thetford Mines chrysotile workers with lung cancer with and without asbestosis.

Characteristic	With asbestosis, 17 cases	Without asbestosis, 5 cases
Demographics[a]		
Median age	69 years	66 years
Mean duration employed	37.8 ± 27 years*	24.7 ± 10 years
Mean latency	46 ± 10 years	40 ± 12.5 years
Cumulative exposure (median MPCFY[b])	284	81
	NS	NS
Median lung fiber content (fibers/μg dry lung, >5 μm long, aspect ratio >3:1)		
Tremolite	62.5*	13.1
Chrysotile	20*	2.9
Optical fibers (phase contrast microscopy)	9429*	2052
Other relevant disease variables		
Other cause of fibrosis present (see text and Tables 3 and 4)	3 of 17 men (17%)	3 of 5 men (60%)
Pleural plaques	10 of 17 men (59%)	1 of 5 men (20%)
Smoking data (means based on data available for 18 of 22 men)		
Years smoked	46 ± 8	46 ± 7
Number of packs per day	1.25 ± 0.5	1.10 ± 1.25
Age when started smoking	16 ± 2.6 years	16 ± 2.0 years

Ns, not significant. [a]Median or mean ± SD. [b]MPCFY: cumulative exposure expressed as million particles/ft^3 from midget impinger counts × total years worked (approximate conversion factor: 1 fiber-year = 3.5 × MPCFY). *$p < 0.05$ (Mann-Whitney or two-sample *t*-test).

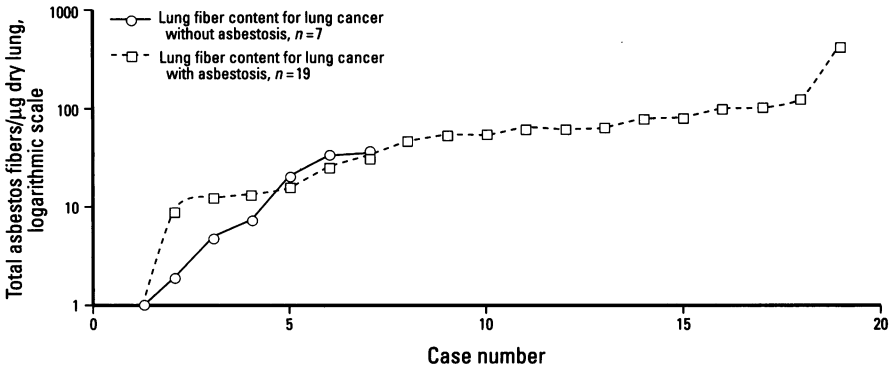

Figure 1. Total lung-retained asbestos fiber in lung cancer cases with and without asbestosis.

Table 3. Exposure parameters in seven chrysotile miners/millers with lung cancer and without asbestosis.

Year started work	Duration of employment, years	Cessation period, years[a]	MPCFY[b]	Tremolite fibers/μg[c]	Chrysotile fibers/μg[c]	Duration or extent of smoking	Pleural plaques	Remarks on autopsy report[d]
1925	47	3	2531	29.6	7.2	44 years	No	Zones of emphysema with very marked fibrosis of lung; asbestos bodies; not asbestosis
1942	37	1	120	2.0	18.4	Unknown	Yes	Diffuse idiopathic interstitial fibrosis with asbestos bodies; not asbestosis
1958	25	0	109.5	0.3	0.5	80 pack-years	No	Very slight fibrosis with a few rare ferruginous bodies; silicotic nodules also present
1925	47	8	80.7	3.2	1.6	14 pack-years	Yes	Some small silicotic nodules. No mention of lung fibrosis; pleural plaques; diffuse pleural thickening
1947	33	1	63	7.3	0.2	Unknown	Yes	No relevant remarks
1939	1	37	44.8	30.8	4.9	Unknown	No	No relevant remarks; bilateral pleural adhesions. Asbestos body digest highest in group
1947	3	30	4.3	1.4	0.5	Unknown	No	Very marked pulmonary fibrosis, mainly silicotic: a few rare asbestos bodies.

[a]Period between end of employment and death with autopsy. [b]Estimates of exposure based on historical midget impinger particle counts (million particles/ft^3 × years). Cases are ranked in descending order of this variable. [c]Fibers of tremolite or chrysotile asbestos longer than 5 μm, aspect ratio 3:1 or greater/μg dry lung. [d]Transcribed from the original French by BW Case.

Table 4. Exposure parameters in seven chrysotile miners/millers with lung cancer and asbestosis.

Year started work	Duration of employment, years	Cessation period, years[a]	MPCFY[b]	Tremolite fibers/μg[c]	Chrysotile fibers/μg[c]	Duration or extent of smoking	Pleural plaques	Remarks on autopsy report[d]
1943	34	1	3.2	7.5	6.5	Unknown	Yes	Moderate asbestosis
1919	8	49	30.9	103.1	2.2	Unknown	Yes	Asbestosis NOS
1946	30	0.9	41.7	22.4	109.2	22 years	No	Moderate to severe asbestosis
1920	47	0.2	110.5	33.6	0.9	54 pack-years	No	Asbestosis NOS
1947	30	0	115.1	5.6	7.1	38 pack-years	Yes	Slight asbestosis
1935	34	13	137.5	21.3	5.1	66 pack-years	Yes	Pulmonary fibrosis; either asbestosis or reactive
1927	36	18	220.4	42	4.7	63 pack-years	Yes	Slight-to-moderate anthraco-asbestotic fibrosis

NOS, not otherwise specified. [a]Period between end of employment and death with autopsy. [b]Estimates of cumulative exposure based on historical midget impinger particle counts (million particles/ft^3 × years). Cases are ranked in ascending order of this variable. Twelve additional cases (not shown) had higher values for cumulative exposure. [c]Fibers of tremolite or chrysotile asbestos longer than 5 μm, aspect ratio 3:1 or greater/μg dry lung. [d]Transcribed from the original French by BW Case.

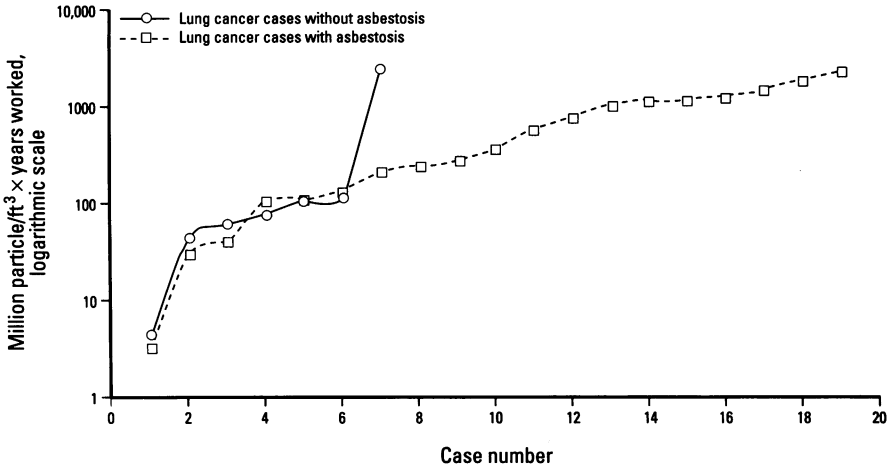

Figure 2. Cumulative exposure in lung cancer cases with and without asbestosis.

retrospective environmental exposure measurements [i.e., median MPCFY as determined by midget impinger counts and applied to job descriptions over the years, as described by McDonald et al. (*9,10*)]. Results were: asbestosis with lung cancer, 385 MPCFY; asbestosis alone, 363 MPCFY; no disease, 161 MPCFY ($p < 0.05$ vs both asbestosis groups); and for the seven lung cancers without asbestosis, 81 MPCFY ($p < 0.01$ vs asbestosis cases without cancer but $p = 0.09$ vs lung cancer cases with asbestosis). Geometric mean comparisons showed an identical pattern, with significantly higher intrapulmonary asbestos fiber concentrations and cumulative exposures in the groups with asbestosis.

Except for the four lung cancer cases in the area of Asbestos, where smoking data were unavailable, comparisons are outlined in Table 2. Patterns are similar to those noted for the combined Thetford and Asbestos workers discussed previously. Almost all parameters associated with asbestos exposure are greater in the group of lung cancers with asbestosis. Note that intrapulmonary chrysotile, as well as tremolite, is significantly increased in lung cancer cases with asbestosis. The excess of both intrapulmonary fiber and cumulative exposure appears to be related to longer duration of employment in those with both diseases. Similarly, those with both asbestosis and lung cancer were more likely to have pleural plaques than those with lung cancer alone.

Differences attributable to smoking were not obvious between the two groups in Thetford Mines (Table 2). Smoking data were available for 18 of the 22 Thetford lung cancer cases and for 47 of the 67 Thetford Mines men without lung cancer. As a whole, the 18 men with lung cancer smoked significantly more than the 47 men who did not have lung cancer. Median values were 58 versus 34 pack-years and 1.3 packs/day versus 0.8 packs per day, respectively; both $p < 0.05$. In binary logistic regression for these 65 men (not shown), smoking was the only exposure variable to show a significant relationship to lung cancer outcome (others entered included asbestosis, cumulative exposure, duration of exposure, and lung fiber concentrations).

These results clearly establish that asbestosis is a good surrogate for asbestos exposure in this group of asbestos-exposed men. This is hardly surprising. Unfortunately, both lung cancer and asbestosis are dose related. Although grouped values show a clear excess of all exposure variables in the lung cancers with asbestosis (Table 2), the practical question with which compensation boards are regularly faced is the attributability of individual cases. To test our hypothesis that overlap between lung cancer cases with and without asbestosis occurs on a variety of exposure variables, we plotted all cases in this analysis against MPCFY (Figure 2), and against total lung-retained asbestos (Figure 1). Inspection of individual values reveals that there is substantial overlap for both measures of exposure. Indeed, in this analysis the lung cancer case with the highest level of MPCFY was one without asbestosis (Figure 2; Table 3).

The presence of asbestosis, however, was no guarantee that lung cancer risk was related to heavy exposure. In Figure 2, it can be seen that three of the lung cancer cases with asbestosis had MPCFY lower than 100, whereas three cases without asbestosis had higher values. This is more fully presented in Tables 3 and 4. It is hard to imagine that a 3-year exposure case with a total of 4.3 MPCFY could have much asbestos-attributable risk, assuming a long smoking history (Table 3). However, it appears that a clinical diagnosis of silicosis may have been missed in this case; the worker's other jobs are not known. It is even more unlikely that the worker with a 47-year employment history, 2531 MPCFY (close to 10,000 fiber-years), and nearly 30 fibers/μg dry lung of tremolite could possibly have a lung cancer unrelated to exposure to asbestos.

Also evident from Table 3 is the capricious nature of the asbestosis diagnosis. Four of the seven cases not diagnosed as asbestosis had lung fibrosis. This was "very marked" in two cases and of diffuse interstitial type in a third case. Of course, asbestos bodies were present, but again the microscopic assessment of these varied. Asbestos bodies were thought to be absent by the pathologist in the case with the highest asbestos body count (in our laboratory) and the highest tremolite fiber count (30.8 fibers/μg dry lung). The case with 37-year exposure, 120 MPCFY, 18.4 chrysotile fibers/μg dry lung, and diffuse interstitial fibrosis with asbestos bodies was called "idiopathic" and likely would not have received compensation. This is notable given the considerable experience of the examining pathologists. Sampling error in routine microscopic assessment of asbestos bodies, decisions about whether such bodies are typical, and decisions about the significance of number and anatomic location of asbestos bodies pose particular problems in chrysotile-exposed workers.

The other side of the coin is evident in Table 4, which shows the seven cases of lung cancer with asbestosis having the lowest values of MPCFY. Three of the seven cases with asbestosis and lung cancer had MPCFY values that fall below one suggested cutoff for causality in this group (*10*). However, in two of these cases, the massive intrapulmonary fiber content (greater than 100 fibers/μg dry lung of either tremolite or chrysotile) suggests that MPCFY estimates were probably wrong. This is especially true in the case with a 49-year gap between last exposure and death. Tables 3 and 4 thus demonstrate that all exposure variables must be examined in the assessment of the individual case.

Discussion

In any autopsy study, the first question that must be asked is whether there has been selection bias, and if so, whether the results may have been influenced. Selection bias was evident in the Sluis-Cremer and Bezuidenhout study (*7*), as they excluded black cases because of poor registration of their histories (*7*), and because exposure and disease incidences were remarkably low for a cohort of amosite workers.

In the current analysis, we must ask whether the cases analyzed are representative of the deaths in the cohort. To assess the possibility of selection bias, we reviewed all the adult autopsies over a 15-year period (1976–1991) in the Thetford Mines Hospital. During this period 676 autopsies were performed on men and women over age 18. Four hundred thirty-eight of the decedents, or 65% of all autopsies—all male—had histories of work in the chrysotile mines or mills. Surveys in the area have indicated that 70% of men over age 60 have such a history. Of the 438 worker autopsies, 155 (35.4%) died of lung cancer and 22 (5%) died of mesothelioma. Over 50% had both asbestosis and pleural changes (plaques or diffuse thickening). Comparable figures in the birth cohort for causes of death among the 2827 deaths from 1976 through 1988 were 11.2% from lung cancer, 0.9% from mesothelioma, and only 1.7% from asbestosis (*10*). For mesothelioma, 66% of all cohort cases had been autopsied. For lung cancer the exact figure is unknown, as hospital autopsies included both cohort and noncohort deaths and the periods do not coincide exactly. A reasonable approximation is 30%. The autopsy rate among the general population of workers is also unknown. In Quebec province, the rate was 10% in 1986, but a previous calculation in the cohort showed a higher overall autopsy rate (17%) among workers up to 1975 (*9*).

It is clear from the above figures that marked selection for possible asbestos-related cancers was taking place among those having autopsies. For asbestosis, the question is less clear, as this is rarely a cause of death. Autopsy rates of asbestosis are probably more representative of the working population than those derived from death certificates unless multiple causes are coded.

Having established that selection bias exists, can we assess its effect on our analysis? The compensation system in Quebec relies heavily on expert consultation by pathologists. It is reasonable to speculate that the increased lung cancer and mesothelioma autopsy rates and numbers are attributable to this factor. An autopsy report is an important part of a compensation dossier, and many autopsies are of the chest only. With regard to our principal hypothesis, this provides larger numbers of cohort autopsies of lung cancer, asbestosis, or neither disease. Could men without previously established and accepted radiological asbestosis be more or less likely to have autopsies? The Quebec compensation board does not currently require asbestosis for the attribution of lung cancer to asbestos exposure. However, since asbestosis itself

is compensable, the possibility remains that families self-selected cases with more ambiguous diagnoses of this disease for autopsy.

Bias is more likely to arise when cases are being selected for analysis. The two series from which our cases were derived differ in this respect. The ascertainment among Asbestos miners and millers autopsied in the Sherbrooke University Hospital (*11*) is nearly complete (22 of 26 consecutive cohort autopsies). Data are available for less than one-third of the 302 cohort members autopsied from 1963 to 1984 in the Thetford Mines/Black Lake study (*12*). In the latter instance, although the selection was ad hoc, could it have been biased in any way that would affect our results? Subjects were chosen consecutively (*11*) or ad hoc (*12*) a number of years ago for analyses having to do with hypotheses different from the current one, and without regard to their disease status. All the men included in these studies were included in the present analysis, so it is unlikely that our selection was based on the men's asbestosis or lung cancer status.

It is evident from the data presented above and in Table 2 that asbestosis, as might be expected, is a good surrogate for asbestos exposure. This is true whether the gold standard used is intrapulmonary fiber (retained dose), cumulative exposure estimates (MPCFY), time-related variables such as duration of exposure, or even the presence or absence of pleural plaques. However, Hughes and Weill (*4*) go much further in stating that asbestosis is a prerequisite for lung cancer attribution in those with asbestos exposure. This statement goes beyond the known facts and relies on mechanistic speculation. The authors believe that asbestosis is produced by a mechanism or mechanisms that will also lead to lung cancer. Their hypothesis requires that the mechanism(s) always be intermediate in that lung cancer always follows asbestosis. Finally, the speculation requires that lung cancer occurring without asbestosis never be caused by asbestos exposure alone (or in synergy with cigarette smoking) regardless of the level of that exposure, and that no mechanism can occur that does not involve intermediate fibrosis. The biological fallacy of this argument has been well documented by Abraham (*14*), Roggli et al. (*15*), and Egilman and Reinert (*5*). It is most evident in the recent consensus of an International Agency for Research on Cancer (IARC) workshop held "... to review and discuss the current knowledge on mechanisms of fiber carcinogenicity, and to formulate recommendations to IARC on the use of such data in the process of evaluation of carcinogenic risks to humans ..." (*3*). This working group concluded simply that "Overall, the available evidence in favor of or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (*3*). On the specific issue of links between inflammation, fibrosis, and cancer, the consensus report noted that in animals the simultaneous appearance of significant numbers of lung tumors and high levels of pulmonary fibrosis "does not necessarily indicate a cause–effect relationship because both processes may be a response to high fiber doses ... There are no data on direct links between inflammation and carcinogenesis" (*3*). Finally, one must remember that lung cancer originates in the large airways while asbestosis is a disease of the lung parenchyma at and beyond the respiratory bronchioles (*15*).

As our analysis indicates, the identification of asbestosis (or its absence) is suspect in many lung cancer cases. This is evident from Tables 2 and 3 and in Case and Sebastien's study (*11*). This is not because of any incompetence on the part of the hospital pathologists, who have more experience in the diagnosis of asbestosis than others in North America and have contributed significantly to the literature on this subject. Particularly striking is the finding that among cases of lung cancer without asbestosis there is an excess of idiopathic diffuse pulmonary fibrosis. This is a result of the difficulty faced by pathologists in identifying asbestos bodies in quantities sufficient to diagnose asbestosis, a real problem in chrysotile-induced disease.

It is clear from the analysis that there is substantial overlap in exposure data between lung cancer cases among asbestos workers with and without asbestosis despite the significant excesses in exposure among groups of asbestotics. We conclude that unless and until it is established that lung fibrosis causes lung cancer, asbestosis cannot be used as the only factor in attribution of lung cancer to asbestos exposure. The normal standards of proof of causality in epidemiology (*5*) and experimental biology (*3*) have not been met for this 60-year-old hypothesis (*1*). To ignore our knowledge of indices of exposure other than the simple presence or absence of asbestosis is simplistic and biologically naive.

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